IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants: Maurice M. MOLONEY, *et al.*

Title: **METHOD FOR PRODUCING AND CLEAVING A FUSION PROTEIN WITH AN N-TERMINAL CHYMOSIN PRO-PEPTIDE**

Appl. No.: 09/402,488 Filing Date: 2/16/2000

Examiner: David J. Steadman Art Unit: 1652

Confirmation Number: 6010

REPLY BRIEF UNDER 37 C.F.R.§ 41.41

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Sir:

Appellant submits this Reply Brief to address the new issues raised in the Examiner's Answer mailed August 17, 2007, including issues associated with the eight new references cited at pages 12-15 and 27-42 of the Examiner's Answer.

Appellant acknowledges with appreciation the withdrawal of the new matter rejections of claims 1, 4-10, 12-16, 18-19, and 50-51, indicated at pages 3-4 of the Examiner's Answer.

This Reply Brief is accompanied with a Request for Oral Hearing and the required fee. If this payment is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any overpayment) to deposit account no. 19-0741.

REMARKS

The Examiner maintains the rejection of claims 1, 4-10, 12-16, 18-19, and 50-51 for alleged lack of enablement with respect to the recombinant production of proteins in animals and plants. *See* Examiner's Answer, pages 8-19 and 25-42. The Examiner cites ***eight new references*** in support of his position, but these references do not undermine the enabling quality of the instant specification with regard to the claims on appeal.

The Examiner acknowledges that "representative examples of recombinant transgenic protein production in rabbits, sheep, goats, cows, pigs and mice were well-known at the time of the invention," and that "representative examples of recombinant transgenic protein production in plants was well-known at the time of the invention." Examiner's Answer, pages 28 and 30. This finding of fact warrants withdrawal or reversal of the enablement rejections. Appellant strongly objects to the Examiner's dismissal of the representative publications submitted by Appellant as "anecdotal," and as somehow not accurately reflecting the state of the art. *See, e.g.,*, Examiner's Answer, page 28. There is simply no basis for the Examiner's decision to discount references that support Appellant's position in favor of other references deemed to be "more relevant to establishing the state of the art," and alleged to undermine enablement. Furthermore, the references credited by the Examiner do not support the enablement rejection, as shown below..

The Examiner cites Dyck at, for example, pages 28, 31-32, and 36 of the Examiner's Answer, and alleges that the eight new references are merely cited to support his interpretation of Dyck. Examiner's Answer, page 15. As explained previously, Dyck itself cites numerous categories of successful transgenic protein production, including transgenic milk ("Foreign proteins are commonly reported to be expressed in transgenic milk at rates of several grams per litre," pg. 395); the blood of transgenic pigs ("[P]igs producing human haemoglobin in their own circulatory system have been produced," pg. 395); methods using retroviruses ("[R]etroviruses have been used to successfully produce transgenic mice and viral integration of recombinant sequences into bovine embryos to produce transgenic calves have been reported," pg. 396); methods using embryonic stem (ES) cells or primordial germ

(PG) cells ("Reviews of the literature indicate that the production of chimeric animals with ES or PG cell technology has been applied successfully in mice, rabbits, pigs, cattle and poultry," pg. 397), and methods using pronuclear microinjection, which Dyck characterizes as being "the most straightforward and consistently successful means of gene transfer for most species" (pg. 397). Indeed, Dyck evaluates various transgenic systems as "bioreactors" for large-scale production of proteins, and is hardly evidence of non-enablement.

The Examiner newly cites Janne (previously cited by Appellant), for example, at pages 29, 31-32, and 37 of the Examiner's Answer, but the thesis of Janne is that "the last few years have witnessed a remarkable progress in this area [transgenic expression in the mammary glands of large animals] and proved the feasibility of the use of 'molecular farming' in high-quantity, low-cost production of valuable therapeutic or industrial proteins." While Janne highlights "challenges" in using farm animals as "bioproducers," it also proposes solutions to those challenges. Moreover, as with many of the other references cited by the Examiner, the "challenges" noted by Janne relate to large-scale, commercial production, which is inapposite to enablement of the instant claims.

The Examiner cites Vain, for example, at pages 30, 32-33, 37, 41 of the Examiner's Answer to support his position vis-à-vis recombinant protein production in plants, but Vain reports that 100% of 95 independently transformed rice plants successfully expressed one of two transgenes, and 87% expressed both transgenes. *See* Abstract. Thus, Vain does not support an assertion that undue experimentation is required to produce transgenic proteins in plants.

At pages 31-32 of the Examiner's Answer, the Examiner relies on six newly cited references, Ristevski, Montoliu, Smith, Cameron and Sigmond, to support his position that the state of the art regarding the generation of transgenic plants and animals was not advanced at the time of filing, and also cites Vain and Potrykus for this point. The Examiner is focusing on isolated statements in these references, however, where their teachings as a whole support enablement, as shown below.

The Examiner cites Ristevski for noting the problem of uncontrolled site of transgene integration, which allegedly could lead to integration into a silent locus or altered tissue specificity. *See* Examiner's Answer, page 13. Yet, Ristevski also teaches that "[t]he problems of random transgene integration and uncontrolled copy number will be overcome by the design of transgenic mouse with controlled transgene integration." Ristevski, page 159, col. 2, section 4.1. Thus, Ristevski does not undermine enablement. Moreover, Ristevski is directed to transgenic mice as models for unraveling gene function; thus, many of the concerns raised by Ristevski are not relevant when the purpose of transgenesis is recombinant protein production.

The Examiner cites Montoliu for allegedly teaching the problem of chromosomal positioning effects that may result in ectopic or undetectable gene expression. *See* Examiner's Answer, page 13. Montoliu, however, actually teaches that these problems have been addressed, noting that "several strategies have been devised to overcome such position effects, including the progressive addition of regulatory elements belonging to the same or to a heterologous expression domain." Montoliu, Abstract. Furthermore, Montoliu points to the use of artificial chromosomes, such as YACs, BACs, and PACs to ensure optimal expression levels and "guarantee the correct expression of transgenes." *Id.* Thus, Montoliu itself is at odds with the Examiner's interpretation.

The Examiner cites Smith for allegedly teaching the problem of uncontrollable transgene integration and the randomness of pronuclear injection. *See* Examiner's Answer, page 13. Yet Smith, at page 7, col. 1, section 3.2, teaches that microinjection has become the most widely used method of germline transgenesis, that the technique "is most established with mice," and "also carried out fairly commonly with other animals including, rats, rabbits, farm-yard animals, and fish." Smith also reports methods of controlling transgene expression and avoiding aberrant expression, and discusses other methods of transgenesis. Thus, Smith does not undermine enablement. Moreover, Smith's particular interest is gene therapy; thus, many of the concerns raised by Smith are not relevant when the purpose of transgenesis is recombinant protein production.

The Examiner cites Cameron for allegedly teaching unpredictable transgene expression. Yet, Cameron focuses on recent progress in efficient transgene expression systems, and current efforts for generating transgenic livestock. Cameron, Abstract. Cameron points out that transgenic livestock, such as transgenic rabbits, sheep, and pigs, were produced by 1985, and transgenic cattle soon followed in 1989. Cameron, pages 253-254. Moreover, Cameron reports that livestock transgenesis has reached commercial stages in, for example, sheep expressing human alpha 1-antitrypsin. Cameron, page 261, col. 2. Cameron's statement that "obtaining high levels of biological active human proteins in the milk [of transgenic animals] ***has not been easy***," Cameron, page 261, col. 2 (emphasis added), does not undermine enablement. Rather, Cameron's acknowledgement that "pharmaceutical farming" has made significant progress demonstrates that recombinant protein production in animals was enabled.

The Examiner cites Sigmund for allegedly teaching "the random nature of transgene insertion." *See* Examiner's Answer, page 15. Sigmund, however, is addressing unpredictable phenotypic effects associated with gene transfer, not any problems associated with recombinant protein production *per se*. Moreover, Sigmund attributes the unpredictable phenotypic effects to genetic heterogeneity among strains used for producing transgenic and knockout mice, Sigmund, Abstract and page 1425, col. 2, and offers "effective experimental strategies" to address the issue. Sigmund, pages 1426-28. Further evidencing the high level of skill in the art, Sigmund emphasizes that "it becomes the responsibility of the investigator to use common sense and design the best possible control experiments . . . to assess whether the phenotype observed in their model is due specifically to the targeted modification or is affected by other loci." Sigmund, page 1428, col. 1. Thus, Sigmund does not support an assertion that undue experimentation is required to produce transgenic proteins in animals.

That Vain does not support the Examiner's position is shown above.

While the Examiner again cites Potrykus at pages 28 and 39-40, Potrykus relates to issues encountered on the road to commercialization, assessing the potential "agronomic utility" of different methods that have been used to effect gene transfer in cereal crops, *see* Potrykus (1990) at page 535, top of left column. Moreover, while Potrykus criticizes a

number of different transgenic methods, it also acknowledges methods that have proven successful, including methods using *Agrobacterium* or agroinfection to transform dicots and methods using protoplasts for direct gene transfer of cereals. *See* Potrykus, page 538, right column entitled "A routine and efficient method for the production of transgenic plants from numerous non-cereal species." In fact, the "*Note added in proof*" at page 542 reports Potrykus' own work to establish "what we believe is proof of the recovery of transgenic offspring of *Indica*-type rice." That work, reported in Datta *et al., Bio/Technology* (1990) 736-40, is said to result in "a simple and reproducible method of transformation of an important food crop." Thus, Potrykus does not undermine the enablement of the present invention with respect to recombinant protein production in plants.

The Examiner newly cites Sang for teaching that "transgenesis techniques in poultry species . . . were highly undeveloped," but Sang is not as pessimistic as the Examiner suggests. Sang explores different approaches to transgenesis in chicks, and evaluates and critiques the different methods. Sang notes that a zygote-based method "enabled development of a method to produce transgenic chickens by microinjection of gene constructs into the zygote, followed by culture to hatch." Sang, at 1180, col. 1. Sang reports the development of an embryo-cell based "method for introduction of blastodermal cells and efficient production of high level chimeras." Sang at 1181, col. 1. Sang also acknowledges successful gene transfer in chicks using viral vectors. For example, Sang notes that "[t]he ability to transduce chick embryos by injection of viral preparations near the blastodermal embryo in new laid eggs . . . was shown to be a simple procedure." Sang at 1182, col. 2. This in no way undermines enablement. While Sang does comment on difficulties encountered with these procedures, many difficulties relate to matters of scale (e.g., efficiency) rather than feasibility. Thus, Sang does not support the enablement rejection.

The Examiner newly cites Mitalipov for stating that "somatic cell cloning has not yet been accomplished in primates," but the same sentence references "the successful production of rhesus monkeys by [nuclear transfer] from embryonic blastomeres." Mitalipov, at 1367, col. 2. Moreover, the authors reference nuclear transfer work by others that resulted in live births. Mitalipov at 1372, col. 1. Thus, Mitalipov does not indicate that recombinant protein production in primates was not enabled as of the filing date of the captioned application.

While acknowledging that animals have been used to successfully produce recombinant proteins in their milk, the Examiner cites Houdebine for allegedly teaching that gene transfer remains a difficult task and the vectors are of unpredictable efficiency. Examiner's Answer, pages 12-13. Yet in the Abstract, Houdebine states, "Improvement of these vectors includes the choice of efficient promoters, introns and transcription terminators, the addition of matrix attached resions (MAR) and specialized chromatin sequences (SCS) to enhance the expression of the transgenes to insulate them from the chromatin requirements." Furthermore, while Houdebine recognizes "[s]everal problems," they are related to using "this process . . . in a large scale." Houdebine, Abstract. Indeed, Houdebine concludes that the production of proteins in transgenic milk is likely to become a commercial reality. Houdebine, Abstract and page 282, col. 2.

The Examiner appears to take the position that Appellant must demonstrate, with specific examples, enablement for all species falling within the claimed genus, but § 112 does not impose such an impossible burden. As noted in MPEP § 2164.08 (citing *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976)), "to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work . . . would not serve the constitutional purpose of promoting progress in the useful arts." Because Appellant has demonstrated that recombinant protein production in a wide variety of non-human hosts (including animals, bacteria, insects and plants) was well-developed at the time the present application was filed, the instant enablement rejection is improper, and should be reversed.

Claims 10, 12, 16, 18 & 51

At pages 30-31 of the Examiner's Answer, the Examiner raises specific concerns about the enablement of claims reciting *in vivo* cleavage of the fusion protein, such as cleavage of the fusion protein in the milk, blood, stomach, gut or kidneys. Appellant responds by pointing out that the specification teaches that inducible promoters can be used to direct protein expression. *See, e.g.,* Specification, page 12, line 37-page 13, line 6. Moreover, those skilled in the art would have known that tissue-specific promoters could be used to express fusion proteins in these cites. Additionally, the specification teaches that an

aspartic protease could be expressed at the same site as the fusion protein, using for example, the same or different expression vectors. *See, e.g.,* Specification, page 12, line 37-page 13, line 6 For cleavage in the stomach, the specification teaches that an aspartic protease could be orally administered in conjunction with the fusion protein. *See, e.g.,* Specification, page 13, lines 7-21. Thus, cleavage of the fusion protein in vivo, such as in the milk, blood, stomach, gut or kidneys, is well enabled by the specification.

CONCLUSION

For at least the reasons discussed above and in Appellant's Appeal Brief, the pending claim rejections should be reversed, and the pending claims allowed to issue.

Respectfully submitted,

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